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EDITORIAL COMMENT

When Is a Double Better Than a TRIPLE?

Stenting in Patients With Atrial Fibrillation*

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Patients with atrial fibrillation needing stents pose one of the greatest challenges in cardiovascular medicine (1). The atrial fibrillation generally warrants anticoagulation, and dual antiplatelet therapy is the established standard of care for patients with stents (2–4). The predominant practice in patients with both indications has been to treat with triple therapy (most commonly aspirin, clopidogrel, and warfarin) for varying durations (5). The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial demonstrated that triple therapy produced a large, but unsurprising increase in bleeding compared with double therapy with clopidogrel and warfarin, but no increases in the number of ischemic or thromboembolic events were detected in 573 patients (6). A recent European consensus document nicely summarized the complexity and number of possible combinations of double and triple therapy for various durations, although relatively sparse randomized data were included to support the recommendations (7).

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In this issue of the *Journal*, Fiedler et al. (8) presented the main results of the ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) trial (8). This open-label study randomized 614 patients with an indication for oral anticoagulation (primarily atrial fibrillation) undergoing drug-eluting stent implantation to either 6 weeks or 6 months of triple therapy with aspirin, clopidogrel, and warfarin, followed by double therapy with aspirin and warfarin thereafter. There was no significant difference in the primary endpoint of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months: 9.8% in the 6-week group versus 8.8% in the 6-month group (hazard ratio: 1.14; 95% CI: 0.68 to 1.91; $p = 0.63$). There was also no significant difference in the secondary combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, or ischemic stroke, although there were few events (12 vs. 13). Similarly, there was no difference in the secondary bleeding endpoint of TIMI major bleeding (16 vs. 12 events).

However, more sensitive metrics of bleeding did find a benefit of the shorter duration of triple therapy. In a landmark analysis of any bleeding from 6 weeks to 6 months according to the Bleeding Academic Research Consortium definition types 1 to 5 (9), there was a significant reduction in bleeding: 13.1% versus 21.8% (hazard ratio: 0.57; $p = 0.01$). The open-label design and differences in clopidogrel prescription or adherence may have somewhat diluted the

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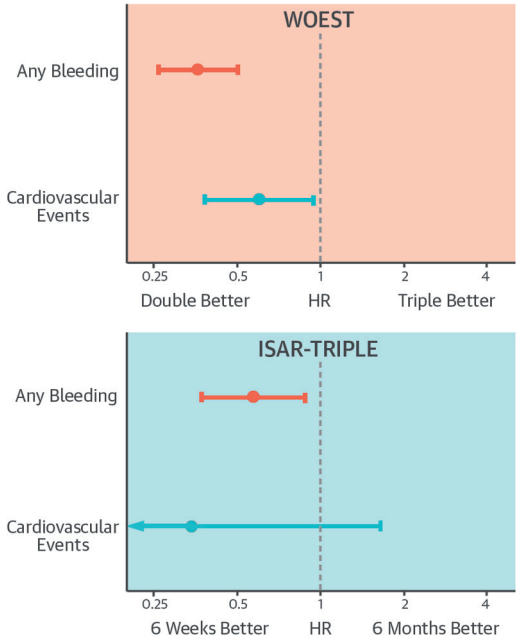
FIGURE 1 WOEST and ISAR-TRIPLE Data Showing Effects on Cardiovascular Events and Any Bleeding Events of Shorter-Duration Triple Therapy (0 or 6 weeks, respectively) Versus Longer-Duration Triple Therapy (12 or 6 months, respectively)



A consistency of results favors the shorter duration. HR = hazard ratio; ISAR-TRIPLE = Intracoronary Stenting and Antithrombotic Regimen–Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting; WOEST = What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting.

contrast between the 2 treatment arms, diminishing the observed bleeding benefit of shorter-duration triple therapy (and also potentially obscuring a benefit of longer-duration triple therapy on thrombotic complications).

In patients on triple therapy, use of prophylactic proton pump inhibition is recommended (although it was used in <40% of the patients in the ISAR-TRIPLE trial) (10,11). The aspirin dose used should be no greater than 100 mg, and, to reduce the gastrointestinal bleeding risk, patients should avoid or minimize use of nonsteroidal anti-inflammatory drugs to the extent possible. To date, warfarin has been the oral anticoagulant agent most used as part of triple therapy, and some experts recommend trying to target an international normalized ratio of 2.0 to 2.5. Use of the novel oral anticoagulant agents instead of warfarin in trials of nonvalvular atrial fibrillation is clearly associated with less intracranial hemorrhage, but there does appear to be at least a signal of excess gastrointestinal bleeding, which is a more frequent cause of major bleeding than intracranial bleeding, as also noted in the ISAR-TRIPLE trial (12).

There are 2 large ongoing trials that should help define the optimal cocktail and duration of antithrombotic agent treatment in patients with atrial fibrillation and recent stents. The PIONEER AF-PCI (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial (NCT01830543) will randomize more than 2,000 patients to 1 of 3 combination regimens. The REDUAL-PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) trial (NCT02164864) will randomize more than 8,000 patients to 1 of 3 combination arms. There are many patients who are eligible for these trials. It is a population that doctors often lament is very common, but there is great uncertainty about the correct treatment. However, this population can be challenging to enroll in clinical trials, and it will be important for physicians to actually support these studies for a definitive answer to be produced. Otherwise, this will be an area that continues to be driven by opinion, instead of by large randomized data sets.

Until such data become available and outside of clinical trials, it is very reasonable to adopt the general strategy supported by the ISAR-TRIPLE trial, and by the WOEST study, which is to abbreviate the duration of triple antithrombotic therapy. Double therapy does seem to beat extended-duration triple therapy (**Figure 1**). Whether that duration of triple therapy should be 0, 4, 6, or 12 weeks, or even longer is uncertain and may be influenced by ischemic, thromboembolic, and bleeding risks. On the basis of the ISAR-TRIPLE study, 6 weeks certainly seems like a reasonable starting point, titrating the duration and intensity of triple antithrombotic therapy upward or downward, depending on patient and lesion characteristics.

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